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PLATELET RICH PLASMA PREVENTS TITANIUM MESH EXPOSURE IN ALVEOLAR RIDGE AUGMENTATION WITH ANORGANIC BOVINE BONE.

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ABSTRACT

Objective:
Bone augmentation with the titanium mesh (Ti-mesh) technique is susceptible to a large rate of complications such as morbidity of bone graft donor site, and mesh exposure to the oral cavity. The purpose of this study was to evaluate the efficacy of anorganic bovine bone (ABB) in alveolar bone augmentation with the Ti-mesh technique, as an alternative to autologous bone grafts. In addition, we investigated the effect of platelet rich plasma (PRP) in preventing mesh exposure, by applying it to cover the Ti-mesh.

Materials and Methods: The 30 patients recruited for this study underwent 43 alveolar bone augmentation with the Ti-mesh technique using in all of them ABB as graft material. In 15 patients the Ti-meshes were covered with PRP (PRP group) while in the other 15 the Ti-meshes were not (control group). After 6 months, patients were called for clinical, radiographic and histological evaluation, and implant placement surgery. A total of 97 implants were placed in the augmented bone and their evolution was followed up for a period of 24 months.

Results:
Significant differences were found between the two study groups in terms of complications and bone formation. In the control group 28.5% of the cases suffered from mesh exposure, while in the PRP group, no exposures were registered. Radiographic analysis revealed that bone augmentation was higher in the PRP group than in the control group. Interestingly, mesh exposure seemed to be a risk factor regarding graft resorption and failure.
Overall, 97.3% of implants placed in the control group and 100% of those placed in the PRP group were successful during the monitoring period.
We suggest that the positive effect of PRP on the Ti-mesh technique is due to its capacity to improve soft tissue healing, thereby protecting the mesh and graft material secured beneath the gingival tissues.

Conclusions: Alveolar bone augmentation using ABB alone in the Ti-mesh technique is sufficient for implant rehabilitation. Besides, covering the Ti-meshes with PRP was a determining factor for avoiding mesh exposure in this study. Titanium mesh exposure provoked significant bone loss, but in most cases it did not affect the subsequent placement of implants.

Key words: anorganic bovine bone, bone regeneration, platelet rich plasma, titanium mesh, exposure.

Clinical Relevance

Scientific rationale:
Osteoconductive properties of ABB have been described in many bone augmentation procedures with good results, so it seemed reasonable to expect similar outcomes when applied in the Ti mesh technique. Although the use of PRP in bone regeneration is a moot question its effects over soft tissue seems to be clearer. In this study we compare both the efficacy of ABB alone and the effect of PRP over soft tissues in the titanium mesh technique.

Principal findings:
ABB alone produces sufficient bone volume augmentation for implant rehabilitation and the use of PRP covering the titanium mesh can improve the soft tissue healing over the titanium mesh preventing its exposure.

Practical implications:
ABB alone is an excellent graft material for the Ti mesh technique that achieves alveolar bone augmentation without the need of autologous graft. Moreover PRP can be an excellent tool for preventing mesh exposure in the Ti mesh technique.

Introduction

Several techniques for alveolar bone augmentation have been described in order to give solution for inadequate alveolar bone volume, which often precludes the ideal placement of dental implants placement (Adell et al 1990, Simion et al 1994, Buser et al 2000, Cordaro et al 2002, Rochietta et al 2008). Onlay grafts and guide bone regeneration (GBR) are widely used for alveolar ridge augmentation prior or simultaneous implant placement. Clinical and histological data support the use of these approaches (van Steenberghe et al 1997, Keller et al 1999, Parma-Benfenati et al 1999). However, the success of GBR procedures seems to be highly technique-sensitive and therefore application to a wide community of operators and clinical settings remains unclear (Simion et al 1994a, Tinti et al 1996, Tinti & Benfenati 1998, Simion et al 2007, Rochietta et al 2008). On the other hand, onlay grafts implies the extraction of an autologous bone block that is often traumatic for the patient.

GBR presents several controversies concerning two aspects: the type of barrier and the type of graft used (Boyne et al 1985, von Arx et al 1996). Regarding the first issue, two principal barriers have been proposed: cell-occlusive membranes and Ti meshes. Cell-occlusive membranes showed very good results obtaining great quantity of regenerated bone, however they have demonstrated two major inconvenients, i) low stiffness for maintaining the contour of the regenerated sites and ii) a high risk of infection after wound dehiscence and barrier exposure (Simion et al 1994a, Simion et al 1994b, Simion et al 1994c). In GBR techniques, soft tissue closure over the augmented area plays an important role in preventing wound dehiscence and bacterial contamination of the exposed membrane. On the other hand GBR using Ti-mesh is a reliable technique with improved stiffness compared to cell occlusive membranes that obtaining predictable results in both width and vertical bone augmentation (Malchiodi et al 1998, Maiorana et al 2001, Artzi et al 2003, Profussaefs et al 2006, Corinaldesi et al 2007, Rocuzzo et al 2004, 2007, Pieri et al 2008).

Although, this technique is much more predictable in width bone augmentation, increase of vertical bone volume has been described even in severe cases, in a predictable way (Table 1).

Early studies advocated the use of autogenous bone in the augmented space beneath Ti meshes (Boyne et al 1985, von Arx et al 1996). Although the autologous bone is considered the gold standard bone substitute because of its intrinsic properties, its availability is restricted by the limited amount of intraoral grafts, the morbidity associated to second surgery at the donor site, and the high cost for bone harvesting

from extraoral sites. Therefore, alternative biomaterials have been developed to substitute autologous bone graft.

Among the available bone substitutes, anorganic bovine bone (ABB) have demonstrated to be the biomaterial with major long-term success reports in the literature used in alveolar bone augmentation techniques. Bio-Oss® (Geistlich Biomaterials; Wolhusen, Switzerland) is a biocompatible and osteoconductive ABB (Benezra *et al* 2002), that provides an ideal scaffold for new bone formation (Hammerle *et al*1998, Piatelli *et al* 1999). It has been extensively used for alveolar bone augmentation (Valentini *et al*2003, Wallace *et al* 2005) with high clinical success rates (Carmagnola *et al* 2003). Accordingly, previous studies have introduce the use of ABB to the Ti mesh technique, either alone , or combined with autologous bone (Maiorana et al 2001, Corinaldesi et al 2007, Pieri et al 2008) (Table 1).

Another major inconvenient of the Ti mesh technique concerns the high rate exposures. These exposures may facilitate graft infection or even loss (Table 1).

PRP is an autologous fibrin adhesive with high platelet concentration easily obtained from whole blood by centrifugation (Antoniades 1981; Marx *et al* 1998, Anitua 1999) Furthermore, PRP has a high concentration of angiogenic and mitogenic growth factors implicated in soft tissue healing, such as TGF (Wijesjo *et al* 1998), PDGF and EGF (Giannobile et al. 1996), and has been recently used to improve soft tissue healing in periodontology. PRP effects could enhance soft tissue healing over the Ti-mesh avoiding its exposure and prevents the derived complications.
In the present study, a clinical trial was performed to evaluate two aspects regarding the Ti mesh technique: i) to examine the outcome of ABB grafting alone, and ii) the benefit of covering the Ti-mesh with PRP, in order to improve soft tissue healing and prevent exposure. The results were obtained by means of clinical investigation, radiographs and histological analysis.

Table 1.Summary of clinical studies reporting the amount bone gained and complications rate using the Ti-mesh technique

Pts/BAP (n/n)	Type of Graft (%)	ABW (mm)	ABH (mm)	ME (%)	Impl (n)	Survival (%)	Success (%)	References
20/20	AB (100)	ID	ID	50	28	ID	ID	Von Arx et al 1996
25/25	AB (100)	5.65	ID	0	120	ID	100	Malchiodi et al 1998
23/23	AB (100) *	ID	5	17.3	ID	ID	ID	Rocuzzo et al 2004
18/18	AB (100) *	ID	4.8	22.2	37	100	100	Rocuzzo et al 2007
14/23	AB/ABB (50/50)	ID	ID	14.2	59	98.3	ID	Maiorana et al 2001
16/19	AB/ABB (70/30)	4.16	3.71	5.3	44	100	100	Pieri et al 2008
12/12	AB/ABB (70/30)	ID	ID	0	35	100	100	Corinaldesi et al 2007
7/7	AB/ABB (ID)	3.71	2.86	57	ID	ID	ID	Profusaefs & Lozana 2004
10/10	ABB (100)	ID	5.2	20	20	100	ID	Artzi et al 2003

Pts: patients; BAP: bone augmentation procedures; ABH: average bone height gained; ABW: Average bone width gained; ME: mesh exposure; Impl: implants placed; ID: Insuficient data;*: block grafts.

Patient and methods

Patients

Before commencing this study, approval was obtained from the ethical committee for clinical trials of the "Hospital San Carlos" (Madrid, Spain), to carry out a pilot clinical study in the dental clinic "Clinica Dental Alcala" (Madrid, Spain). Patients were enrolled in the study on the basis of having insufficient bone height (< 7 mm), width (< 3 mm) or both, in either maxilla or mandible (Figure 1).
Patients who need contemporary sinus floor augmentation or nasal floor augmentation where included, while smokers (>10 cigarets per day) and patients with severe systemic disease (ASA (III or IV) – American Society of Anesthesiology) were excluded. Informed written consent to participate in this study was obtained from all patients after explaining the objectives and protocol of the study, and possible side effects.

During the study period (from May 2003 to September 2008) 209 patients attended the dental office demanding implant treatment. Among these patients, 30 were recruited for this randomized controlled clinical trial. The study group constituted by 17 females and 13 males with age range between 48 and 76 years old.
There was heterogeneity in the systemic diseases present in some of the selected patients, such as diabetes, heart failure and osteoporosis; however, none of these conditions are known to jeopardize implant´s success (Mombelli *et al* 2006).

Figure 1. Summarize the average residual bone height and width, the site of intervention and type of GBR procedure performed on the patients included in the study. Most of the procedures involved situations with extended tooth gaps and distal extension, and combined vertical and horizontal bone augmentations.

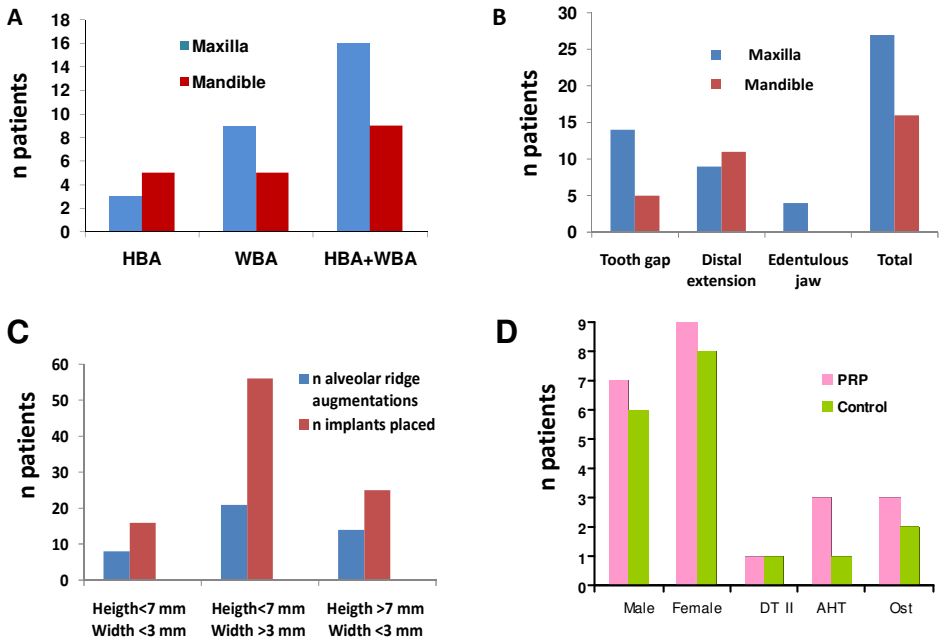

Fig 1. Distribution of: patients as a function of bone augmentation procedure (A); patients as function of treatment site (B); treatment procedures as function of residual bone graft size

(C); and patients by medical situation and treatment group (D). HBA: height bone augmentation; WBA: width bone augmentation. DT II: Type II diabetes; ATH: arterial hypertension; Ost: osteoporosis.

Randomization

Patients included in the clinical trial were randomly allocated by a blinded assistant in two groups, the first was to be treated with PRP covering of the Ti-mesh (PRP group), while the second one did not receive the PRP treatment (control group). Allocation of participants to intervention groups in a truly unpredictable, randomized sequence was performed by computerized random number generated using GraphPadQuickCalc software (GraphPad Software Inc., La Joya, CA), including the concealment of the allocation schedule until the assignment was made. Subject numbers were assigned at the baseline examination in consecutive order by the principal investigator. The sample size used has been usual in pervious studies for this type of clinical evaluation (Table 1). The presence of systemic disorders was registered and its distribution was balanced among the two treatment groups (Figure 1D).

Blinding

The surgeon was blinded to the graft covering material applied to each patient before graft implantation. An assistant handled the PRP or nothing once the Ti-meshes were placed.

Platelet rich plasma

PRP was prepared according to the Anitua's method[15] (Anitua 1999). Blood was collected from all patients 30 minutes before starting the surgery to ensure the blinding of the surgeon. In the PRP group, between 10-20 ml of blood was withdrawn via venous aspiration into 4.5 ml test tubes and mixed with a 3.8 % sodium citrate solution at a ratio 5/1 (v/v) achieving anticoagulation through calcium binding. The blood was then centrifuged with a Bti® PRGF System II centrifuge (Bti Biotechnology Institute S.L, Vitoria, Spain) into three basic components: red blood cells (RBCs), PRP, and platelet poor plasma (PPP) (Figure 2A). Because of the different densities of the components, the RBC layer forms at the bottom of the tube, the PRP layer in the middle, and the PPP layer at the top. A pipette (Gilson Inc., Middleton, WI) was used to separate the layers, from the less dense to the denser. Therefore PPP was separated first (about 2.25 ml followed by PRP (about 0.9 ml), leaving as residual the RBCs layer (about 2.25 ml) (Figure 2B).

Surgical protocol

An alveolar ridge augmentation was performed in all patients following the method described by Boyne et al (1985) and Von Arx et al (1996).

Under local anesthesia a mid-crestal with divergent buccal incisions was performance to allow elevate two mucoperiosteal flaps to the buccal and palatal aspects. Perforations into de marrow space were produced. In all patients ABB particles were adapted to the

deficient ridge and a Ti-mesh that was individually trimmed previously was placed over the grafts and fixed with micro-screws. Subsequently PRP was used as a membrane covering the Ti-meshes in the PRP group, while nothing was added to cover the Ti-mesh in the control group (Figure 3). Then released periosteal incisions were made and a tension free, tight wound closure was accomplished. Postoperatively, antibiotics, anti-inflammatory and antiseptics were prescribed, and sutures were removed 1 week after surgery. Patients were instructed not to wear their prosthesis for 6 months after surgery to avoid transmucosal pressure on the augmented area. All patients were required to follow a soft diet.A healing time of 6 months was allowed before implant placement (Osseotite, Biomet 3i Inc, Palmbeach, FL). A representative case with this reconstructive method is presented (Fig 3).

Radiographical analysis

Radiographs (orthopantomography) and computed tomographies (CT) of the treated sites were taken before treatment, and six months postoperatively. The bone volume was quantified in both PRP and control groups using the SIMPlant 7.0 software (Columbia Scientific, Columbia, MD). Three selected zones in each alveolar ridge augmentation were chosen for standardized evaluation. Differences between preoperative and postoperative bone height and width were measure to assure the alveolar bone augmentation obtained. (Pieri et al 2008). Implant osteintegration and success was assessed by radiographical analysis of the implanted sites 6 months after their placement.

Histological analysis

The histological analysis was performed in 2 patients of each group. After a healing period of 6 months, these patients were called for implant placement and biopsies were retrieved from the treated sites using a trephine burr (Ø = 3.0 mm x 10.0 mm in length). Subsequently the biopsies were fixed in a 10% formaldehyde (pH 7.4) and stored at 4ºC. After dehydration in ascending series of alcohol (60 to 100 %), biopsies were embedded in 2-hidroxy-ethyl-methacrylate (Technovit, Leica Microsystems GMBH, Wetzlar), then polymerized into ready-to-cut sample blocks.

A saw microtome (1200 Leica, Leica Microsystems GmbH, Wetzlar, Germany) was used to cut 15 µm thick histological sections from the blocks. Afterwards, surface staining was performed with basic fuchsine and methylene blue (Donath & Breuner 1982). The histological evaluation of bone neoformation was carried out by means of optical microscopy.

Statistical analysis

The distribution of patients' systemic conditions (diabetes, smoking, etc…) among clinical treatments' groups was assessed using the chi-square test, in order to evaluate comparability between groups. Moreover two-way ANOVA tests, in the univariate analysis were used to find any association between patients' treatment, the Ti-mesh exposure, and treatment success. A statistical software package (SPSS 17.0 Chicago, IL) was used for the statistical analysis.

Results

The bone augmentation, and implant placement procedures performed in this study are summarize in Table 2.

Mostly, healing was uneventful in all patients since none of them complained of significant pain and no signs or symptoms of infection were reported.
Successful alveolar ridge augmentations allowed the installation of one to three rough-surfaced implants per site (Osseotite, Biomet 3i Inc, Palmbeach, FL) with diameters of 3.3-4.0 mm and lengths of 10.0-13.0 mm.
During the 24 month follow up period, one case of graft failure and another of implant failure were registered in the control group, while the PRP group presented no complications (see Table 2 and 3). Moreover, the amount of bone height and width gained was higher in patients treated with PRP (Table 2).
Successful implants were uncovered for fixed prosthetic rehabilitation and no implant complications were registered beyond this point.

Table 2. Distribution of patients, alveolar ridge augmentations, complications and implants by Ti-mesh covering

Treatment group	*n patients/ n grafts*	*Graft complications (%)*		*ABH (mm)*	*ABW (mm)*	*ABHL*	*ABWL*	*Impl$_{failed}$/ Impl $_{total}$*	*Impl Survival (%)*
		Mesh exposure	*Failure*						
PRP	15/22	0.0**	0.0	3.5±0.7**	4.1±0.6**	0.5±0.6	NRA	0/51	100
Control†	15/21	28.5 [16.6]*	4.0	3.1±0.8 [2.3±0.2]*	3.7±0.6 [3.1±0.2]*	0.7±0.6 [1.1±0.9]*	NRA [0.6±0.5]*	1/46 [0/12]	97.3 [100]
Total	30/43	14.0	2.3	3.3±0.2	3.9±0.2			3/97	98.6

*ABH: Average bone height gained; ABW: Average bone width gained; Impl: Implants placed; ABHL: Average bone height loss; ABWL: Average bone width loss; NRA: No radiografically appreciated; † patient who loss complete graft was excluded from statistical analysis. [] Values for exposed meshes. **Significant differences between PRP and control groups (p<0.05).* Significant differences between exposed and non exposed meshes (p<0.05).*

Histological observations

Histological analysis of the regenerated sites revealed the presence of mineralized newly formed bone growing beneath the Ti-mesh, surrounding the un-resorbed ABB granules (Figure 5). Its is important to notice the absence of fibrous tissue and the complete enclosure of ABB granules within the new bone. These observations confirm the validity of ABB in regenerating bone beneath Ti-meshes for GBR.

Surgical complications

The main complication registered during the study was Ti-mesh exposure (Figure 6). This condition was observed in 6 cases, all belonging to the control group (Table 3). In 5 of these cases, the exposure area were small (≤ 10 mm^2) while in one patient a large exposure area took place (>10 mm^2). Ti-mesh exposure proved to be a risk factor

regarding partial resorption or complete loss of the grafts (Table 2). Interestingly, no Ti-mesh exposures, or implant failures were observed in the PRP group.

Table 3. Detail of patients with Ti-mesh exposure

Gender	*Age (years)*	*Preoperative Bone Height & Width (mm)*		*Ti-mesh exposure (mm^2)*	*Postoperative Bone Height & Width (mm)*		*Implants' Position*
		Pre-BH	*Pre-BW*		*Post-BH*	*Post-BW*	
M	55	10	3	<10	10	5.5	13,23
F	42	9	2.5	<10	11.5	5.5	24,26,27
F	62	8	6	<10	10	6	46,47
F	58	9	4	<10	11.5	6.5	35,37
F*	51	5	7	<10	5	7	46*
M†	69	10	3	>10†	10	5.5	23,24

* In this patient infection and total graft loss occurred, but still a 6.0 mm long x 5.0 mm wide implant was placed leaving the upper machined part of the implant over the bone residual bone crest.

† Large exposure area of the Ti-mesh, but it did not prevented implant placement

Survival of grafts

Pre and postoperative bone volume were measure and compared between groups, and also between patients with Ti-mesh exposure versus no Ti- mesh exposed patients for statistical analysis. Vertical bone volume augmentation was defined as the distance between the top of the Ti-mesh and the highest point of the crest postoperatively, while the horizontal bone volume augmentation was measure by the distance between the most buccal point of the residual bone and the Ti-mesh. The radio-opacity of ABB made easy the difference between the residual bone and the new regenerated bone (Figure 3).

Evaluation of graft loss was achieved by measuring the black space between the mesh and the new regenerated bone. Although a higher incidence of graft loss occurred in the control group, no statistical differences were observed between the two groups. However, Ti-mesh exposure provoked significant increase of graft loss in the control patients (Table 2).

Graft survival at the secondary surgery was sufficient to allow implant placement in all the patients included in the study except one in which an implant 5.0mm x6.0 mm were placed because a completely loss of the graft. However, we found that in five cases partial loss of bone graft occurred probably because of Ti-mesh exposure (Table 2).

All patients with PRP treatment did not showed Ti-mesh exposure while patients with no PRP treatment showed a significantly higher incidence (28%) of Ti-mesh exposures (Table 2 and 3). Also vertical and horizontal bone volume augmentation, were significantly slightly higher in the PRP group ($p<0.05$).

Implant survival rates

Implant survival was defined as the percentage of implants remaining in situ during the entire observation period. In this study over 97 implants were placed, 95 remain in situ, and 2 failed in the control group, which gave a 97.5% implant survival rate (Table 2). We did not found differences between the PRP and control groups in terms of implant survival, and mesh exposure did not affect implant success as well.

Discussion

Early studies on the Ti-mesh technique based on the use of autologous bone achieved promising results in augmented bone volume and implant survival (Table 1). However the use of autologous bone is restricted by its associated of morbidity, surgical cost, and limited amount of intraoral grafts.

Recent studies (Maiorana et al 2001; Profussefs & Lozana 2006; and Pieri et al 2008) proposed the combination of autologous bone with ABB in order to reduce the need of bone harvesting from patients. These procedures achieved positive results that encouraged consequent assays evaluating the potential of using ABB alone in Ti mesh vertical bone augmentations (Table 1).

In this study ABB alone achieved similar results to those previously described for autologous grafts Ti mesh GBR. Our results suggested that vertical and horizontal bone augmentation with Ti-mesh using ABB alone as graft material is predictable and has a low incidence of major complications. These results have major implications, thus by eliminating the need for autologous grafts in GBR procedures a larger scope of patients may be treated. Moreover, unlike autologus grafts, ABB grafts proved to be the dimensionally stable during the two year follow up period. Probably due the combination of biocompatibility, osteconductivity, and low resorption properties of ABB in vivo (Schlegel et al, 2003, Zitmann et al 2001).

Ti-mesh exposure has been correlated to subsequent complications such as graft resorption and loss, often impairing implant treatment (Von Arx, 1996). These facts were confirmed in this study, since graft resorption and loss occurred only in cases were exposure of the Ti mesh took place.
The patients of the control group suffered from a rate of complications, similar to that reported in the previous literature for GBR with autologous graft and Ti meshes (Table 1 and 2). On the other hand, the incidence of Ti mesh exposure was completely eradicated in the PRP treated group (Table 2).

It was observed that soft tissue healing was better when PRP was applied over the Ti-mesh compared to controls without PRP coverage. This was likely to translated into an improved gingival biotype and subsequent important resistance to Ti-mesh exposure.

There is a large controversy regarding the usefulness of PRP in bone regeneration procedures (Torres et al 2009). Many studies have shown that PRP is unable to influence bone growth in cavities and defects. However, most of the dental literature has been focused on evaluating its effect on hard tissues, ignoring potential benefits on surrounding soft tissues.

PRP may enhance soft tissue healing by concentrating large amounts of fibrin and growth factors secreted by platelets, that increases both angiogenesis and fibroblast cell

differentiation (Tamimi et al 2007). PRP increases early wound strength, by reducing the inflammatory phase of wound healing allowing early deposition of collagen, glycosaminoglycan and fibronectin. Moreover, PRP has also been found to decrease in patient morbidity and pain (Bathusky & Wang 2008).

Interestingly, gingival healing seemed to have an effect on the underlying bone formation. Bone grafts in the control group experience resorption beneath the Ti-mesh, while in the PRP group the amount of augmented bone was higher and no graft resorption was observed. However, we believe this phenomenon occurs mainly due to soft tissue protection rather than by direct effect on bone formation.

Conclusion

The results of the present study demonstrated that ABB alone may be used as graft material in the Ti-mesh technique with predictable results for localized ridge augmentation in humans. Moreover, applying PRP over the Ti mesh, achieved a major reduction in complications such as graft failure, graft resorption and mesh exposure.

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